

## Title (en)

PYRIMIDINE HYDROXY AMIDE COMPOUNDS AS PROTEIN DEACETYLASE INHIBITORS AND METHODS OF USE THEREOF

## Title (de)

PYRIMIDINHYDROXY-AMIDVERBINDUNGEN ALS PROTEINDEACETYLASE-HEMMER UND VERWENDUNGSVERFAHREN DAFÜR

## Title (fr)

COMPOSÉS D'HYDROXYPYRIMIDINE AMIDE UTILISÉS COMME INHIBITEURS DE LA PROTÉINE DÉACÉTYLASE ET LEURS PROCÉDÉS D'UTILISATION

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## Application

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## Abstract (en)

The present invention relates to novel pyrimidine hydroxy amide compounds, and the use of such compounds in the inhibition of HDAC6 and in the treatment of various diseases, disorders or conditions related to HDAC6.

## IPC 8 full level

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## Citation (applicant)

- US 6099562 A 20000808 - DING NI [US], et al
- US 5886026 A 19990323 - HUNTER WILLIAM L [CA], et al
- US 5304121 A 19940419 - SAHATJIAN RONALD [US]
- US 6517889 B1 20030211 - JAYARAMAN SWAMINATHAN [US]
- US 6273913 B1 20010814 - WRIGHT CAROL [US], et al
- US 6258121 B1 20010710 - YANG DACHUAN [US], et al
- US 6251136 B1 20010626 - GURUWAIYA JUDY A [US], et al
- US 6248127 B1 20010619 - SHAH CHIRAG B [US], et al
- US 6231600 B1 20010515 - ZHONG SHENG-PING [US]
- US 6203551 B1 20010320 - WU STEVEN Z [US]
- US 6153252 A 20001128 - HOSSAIN SYED F A [US], et al
- US 6071305 A 20000606 - BROWN JAMES E [US], et al
- US 5891507 A 19990406 - JAYARAMAN SWAMINATHAN [IN]
- US 5837313 A 19981117 - DING NI [US], et al
- US 2001027340 A1 20011004 - WRIGHT CAROL [US], et al
- SCHREIBER ET AL., J. AM. CHEM. SOC., vol. 112, 1990, pages 5583
- MITCHISON, CHEM. AND BIOL., vol. 15, 1994, pages 3
- MARKS ET AL., NATURE REVIEWS CANCER, vol. 7, 2001, pages 194
- JOHNSTONE ET AL., NATURE REVIEWS DRUG DISCOVERY, 2002, pages 287
- HASSIG ET AL., CURR. OPIN. CHEM. BIOL., vol. 1, 1997, pages 300 - 308
- WARRELL ET AL., J. NATL. CANCER INST., vol. 90, 1998, pages 1621 - 1625
- TAUNTON ET AL., SCIENCE, vol. 272, 1996, pages 408 - 411
- YANG ET AL., J. BIOL. CHEM., vol. 272, 1997, pages 28001 - 28007
- GROZINGER ET AL., PROC. NATL. ACAD. SCI. U.S.A., vol. 96, 1999, pages 4868 - 4873
- KAO ET AL., GENES DEV., vol. 14, 2000, pages 55 - 66
- HU ET AL., J. BIOL. CHEM., vol. 275, 2000, pages 15254 - 15264
- VENTER ET AL., SCIENCE, vol. 291, 2001, pages 1304 - 1351
- MEINKE ET AL., J. MED. CHEM., vol. 14, 2000, pages 4919 - 4922
- MEINKE ET AL., CURR. MED. CHEM., vol. 8, 2001, pages 211 - 235
- JOHNSTON JA ET AL., J CELL BIOL., vol. 143, 1998, pages 1883 - 1898
- JUNN E ET AL., J BIOL CHEM., vol. 277, 2002, pages 47870 - 47877
- NOTTERPEK L ET AL., NEUROBIOL DIS., vol. 6, 1999, pages 450 - 460
- ANTON LC ET AL., J CELL BIOL., vol. 146, 1999, pages 113 - 124
- GARCIA- MATA R ET AL., J CELL BIOL., vol. 146, 1999, pages 1239 - 1254
- DUI JL ET AL., J CELL BIOL., vol. 152, 2001, pages 705 - 716
- GARCIA-MATA R ET AL., J CELL BIOL., vol. 146, 1999, pages 1239 - 1254
- KAWAGUCHI Y ET AL., CELL, vol. 1, no. 15, 2003, pages 727 - 738
- ADAMS, J. NAT REV CANCER., vol. 4, 2004, pages 349 - 360
- HIDESHIMA T ET AL., CANCER RES., vol. 61, 2001, pages 3071 - 3076
- KOPITO RR; SITIA R., EMBO REP., vol. 1, 2000, pages 225 - 231
- MANETTO V ET AL., AM J PATHOL., vol. 134, 1989, pages 505 - 513

- SULLIVAN ML ET AL., J. HISTOCHEM. CYTOCHEM, vol. 51, 2003, pages 545 - 548
- LANGLEY B ET AL., CURRENT DRUG TARGETS--CNS & NEUROLOGICAL DISORDERS, vol. 4, 2005, pages 41 - 50
- S. M. BERGE ET AL.: "pharmaceutically acceptable salts in detail", J. PHARMACEUTICAL SCIENCES, vol. 66, 1977, pages 1 - 19
- "Design of Prodrugs", 1985, ELSEVIER
- "Methods in Enzymology", vol. 4, 1985, ACADEMIC PRESS
- "Design and Application of Prodrugs, Textbook of Drug Design and Development", 1991, pages: 113 - 191
- BUNDGAARD ET AL., JOURNAL OF DRUG DELIVER REVIEWS, vol. 8, 1992, pages 1 - 38
- BUNDGAARD, J., PHARMACEUTICAL SCIENCES, vol. 77, 1988, pages 285
- "Prodrugs as Novel Drug Delivery Systems", 1975, AMERICAN CHEMICAL SOCIETY
- BERNARD TESTA; JOACHIM MAYER: "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology", 2002, JOHN WILEY AND SONS, LTD.
- ADVANCED DRUG DELIVERY REVIEWS, vol. 19, 1996, pages 1 15
- J. MED. CHEM., vol. 39, 1996, pages 10
- SAULNIER ET AL., BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 4, 1994, pages 1985
- T. W. GREENE: "Protecting Groups in Organic Chemistry", 1999, JOHN WILEY AND SONS, INC
- JACQUES ET AL.: "Enantiomers, Racemates, and Resolutions", 1981, JOHN WILEY & SONS
- R. LAROCK: "Comprehensive Organic Transformations", 1989, VCH PUBLISHERS
- T.W. GREENE; P.G.M. WUTS: "Protective Groups in Organic Synthesis", 1991, JOHN WILEY AND SONS
- L. FIESER; M. FIESER: "Fieser and Fieser's Reagents for Organic Synthesis", 1994, JOHN WILEY AND SONS
- "Encyclopedia of Reagents for Organic Synthesis", 1995, JOHN WILEY AND SONS
- GREGORY ET AL., J CLIN ONCOL, vol. 10, 1992, pages 334 - 342
- ATTAL, M. ET AL., N ENGL J MED, vol. 349, 2003, pages 2495 - 2502
- HIDESHIMA, T.; ANDERSON, K. C., NAT REV CANCER, vol. 2, 2002, pages 927 - 937
- HIDESHIMA, T.; ANDERSON, K. C., NAT REV CANCER, vol. 2, 2002, pages 927 - 937
- HIDESHIMA ET AL., CANCER RES, vol. 61, 2001, pages 3071 - 3076
- MITSIADES, N. ET AL., PROC NATL ACAD SCI USA, vol. 99, 2002, pages 14374 - 14379
- HIDESHIMA, T. ET AL., J BIOL CHEM, vol. 277, 2002, pages 16639 - 47
- MITSIADES, N. ET AL., BLOOD, vol. 101, 2003, pages 2377 - 80
- CHAUHAN, D. ET AL., CANCER RES, vol. 63, 2003, pages 6174 - 6177
- HIDESHIMA, T. ET AL., BLOOD, vol. 101, 2003, pages 1530 - 1534
- HIDESHIMA, T. ET AL., ONCOGENE, vol. 22, 2003, pages 8386 - 8393
- HIDESHIMA, T. ET AL., ONCOGENE, vol. 23, 2004, pages 8766 - 8776
- HIDESHIMA, T. ET AL., CANCER RES, vol. 61, 2001, pages 3071 - 3076
- HIDESHIMA, T. ET AL., ONCOGENE, vol. 20, 2001, pages 4519 - 4527
- RICHARDSON, P. G. ET AL., NENGLJMED, vol. 348, 2003, pages 2609 - 2617
- CHAUHAN, D., CANCER RES, vol. 63, 2003, pages 6174 - 6177
- HIDESHIMA, T. ET AL., ONCOGENE, vol. 23, 2004, pages 8766 - 8776
- "Remington's Pharmaceutical Sciences", 1980
- "REMINGTON'S PHARMACEUTICAL SCIENCES", 1985, MACK PUBLISHING COMPANY
- "Percutaneous Penetration Enhancers", 1995, CRC PRESS, INC.
- BUYUKTIMKIN ET AL.: "Chemical Means of Transdermal Drug Permeation Enhancement in Transdermal and Topical Drug Delivery Systems", 1997, INTERPHARM PRESS INC.
- "The Merck Manual", 1999

#### Citation (search report)

- [X] WO 2008055068 A2 20080508 - METHYGENE INC [CA], et al
- [X] WO 2010080996 A1 20100715 - CURIS INC [US], et al
- [X] WO 2010009155 A2 20100121 - GILEAD COLORADO INC [US], et al
- [X] WO 2004052869 A1 20040624 - HOFFMANN LA ROCHE [CH]
- [X] WO 2007022638 A1 20070301 - METHYLGENE INC [CA], et al
- [X] WO 2006123121 A1 20061123 - CHROMA THERAPEUTICS LTD [GB], et al
- [X] WO 2005030705 A1 20050407 - METHYLGENE INC [CA], et al
- [X] US 3549633 A 19701222 - GRABOWSKI EDWARD J J, et al
- [X] WO 2005012261 A1 20050210 - BASF AG [DE], et al
- [X] WO 03076430 A1 20030918 - JANSSEN PHARMACEUTICA NV [BE], et al
- [E] EP 2524918 A1 20121121 - CT NAC INVESTIGACIONES ONCOLOGICAS CNIO [ES]
- [Y] WO 2007091703 A1 20070816 - ASTELLAS PHARMA INC [JP], et al
- [YP] WO 2011011186 A2 20110127 - UNIV ILLINOIS [US], et al
- [X] FOKS H ET AL: "INVESTIGATIONS ON PYRAZINE DERIVATIVES PART II. SYNTHESIS AND TUBERCULOSTATIC ACTION OF SOME 6-ALKYLAMINOPYRAZINE-2-CARBOXYLIC ACIDS", DISSERTATIONES PHARMACEUTICAE AND PHARMACOLOGICAE, WARSZAW, PL, vol. 24, no. 6, 1 January 1972 (1972-01-01), pages 577 - 583, XP008016985, ISSN: 0012-3870
- [X] ANGIBAUD P ET AL: "Discovery of pyrimidyl-5-hydroxamic acids as new potent histone deacetylase inhibitors", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 40, no. 6, 1 June 2005 (2005-06-01), pages 597 - 606, XP027857726, ISSN: 0223-5234, [retrieved on 20050601]
- [XP] HARISH RAJAK ET AL: "2,5-Disubstituted-1,3,4-oxadiazoles/thiadiazole as surface recognition moiety: Design and synthesis of novel hydroxamic acid based histone deacetylase inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 21, no. 19, 3 August 2011 (2011-08-03), pages 5735 - 5738, XP028286354, ISSN: 0960-894X, [retrieved on 20110808], DOI: 10.1016/J.BMCL.2011.08.022
- [X] FOKS H ET AL: "Studies on Pyrazine Derivatives", POLISH JOURNAL OF PHARMACOLOGY AND PHARMACY, WARSZAW, PL, vol. 26, 1 January 1974 (1974-01-01), pages 537 - 542, XP009176372, ISSN: 0012-3870

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SG 10201509324Q A 20151230; SG 190211 A1 20130628; US 2014142104 A1 20140522; US 2017096403 A1 20170406;  
US 9409890 B2 20160809; WO 2012068109 A2 20120524; WO 2012068109 A3 20120802

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**US 201113296748 A 20111115;** AU 20111329028 A 20111115; AU 2016266069 A 20161202; BR 112013011868 A 20111115;  
CA 2818125 A 20111115; CL 2013001381 A 20130515; CN 201180055168 A 20111115; CN 201610911460 A 20111115;  
EA 201390711 A 20111115; EA 201691121 A 20111115; EP 11840803 A 20111115; EP 16150961 A 20111115; ES 11840803 T 20111115;  
HK 14102178 A 20140304; IL 22632613 A 20130513; IL 24959416 A 20161215; JP 2013539949 A 20111115; JP 2016157532 A 20160810;  
KR 20137015474 A 20111115; MX 2013005392 A 20111115; NZ 61022511 A 20111115; NZ 71040511 A 20111115;  
PH 12015500832 A 20150416; PL 11840803 T 20111115; PT 11840803 T 20111115; SG 10201509324Q A 20111115;  
SG 2013035498 A 20111115; US 2011060791 W 20111115; US 201314082472 A 20131118; US 201615203023 A 20160706